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PMMA to Stabilize Bone and Deliver Antineoplastic and Antiresorptive Agents

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Antineoplastic and antiresorptive drugs added to polymethylmethacrylate cement may prevent local cancer progression and failure of reconstructive devices used to treat patients with pathologic fractures. We tested the mechanical properties of cement containing various amounts of the drugs and found that as much as 2 g of either doxorubicin or pamidronate can be added to Simplex® cement and the cement retains 87% of its compressive and tensile strength after 6 months of wet storage. Approximately 1 mg pamidronate elutes from experimental pellets. One half of the drug elution occurs within the first day in experiments that combined doxorubicin and pamidronate, and within 3 days when pamidronate was the only additive. Cement containing these drugs seems to be strong enough, but its fatigue strength should be tested before using it clinically. Sufficient amounts of the tested drugs elute to have potential biologic activity.

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Despite major improvements that have been made in the local treatment of bone tumors, local failure still occurs. Although not approved by the Food and Drug Administration for this purpose, polymethylmeth-acrylate (PMMA) is the most appropriate local delivery system for drugs that address the serious problems that face orthopaedic oncologists: infection, tumor recurrence, and prosthetic failure from aseptic loosening (Fig 1). We reviewed the existing information regarding PMMA as a drug delivery system and present new data regarding the in vitro performance of cement formulated with doxorubicin or pamidronate, a bisphosphonate with mild antineoplastic capabilities, or both.

Cements containing antibiotics are available commercially internationally, and routinely are hand-mixed in many operating rooms throughout the United States.[4,5,10,14,20,22,25,34,36,43,47,53] Little information exists on PMMA as a delivery vehicle for other drugs that have potential use in oncology.[16,24,31,37,57,58] Because most patients with pathologic fractures from bone metastases have a limited life-expectancy yet sustain frequent failure of their orthopaedic reconstructions, they are suitable for early phase investigational studies of the cement and drug formulations.

Three circumstances make local drug delivery compelling: local tissue ischemia impairs drug delivery, the therapeutic index of the drug is enhanced by increasing the local activity or reducing the systemic toxicity of the drug, or the most

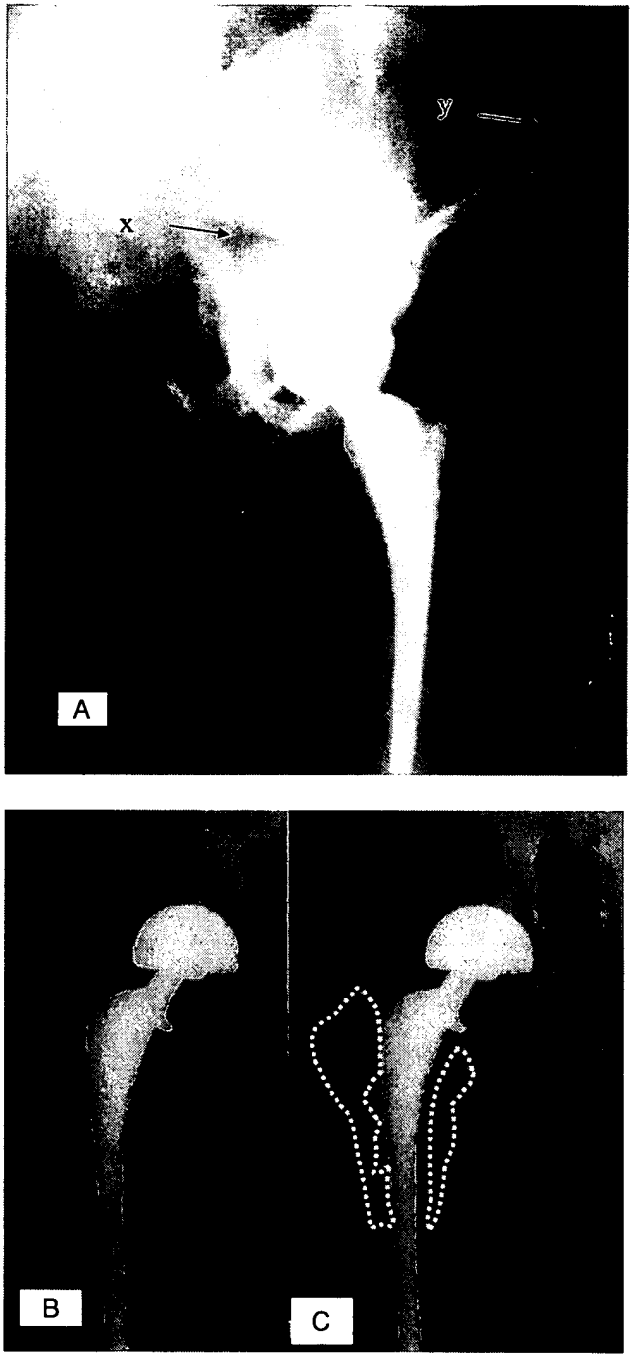


Fig 1A–C. These radiographs show examples of how cancer progression causes bone loss and implant failure despite radiation, systemic bisphosphonates, and chemotherapy in each case. Local antineoplastic agents or bisphosphonates may have prevented the problem. (A) This cemented pelvic reconstruction failed when the tumor in the central acetabulum causing a displaced fracture (x) loosened the screw that supported the implant (y), and the ischium fractured (z). (B) This patient had a successful cemented long-stemmed hemiarthroplasty that became painful 8 months later when the renal cancer destroyed the subtrochanteric femur and disturbed the fixation. (C) The white dotted lines define the area where tumor progression destroyed the bone.

convenient method to administer the drug is local or topical. Classic examples of the first indication are avoidance of doxorubicin's cardiac toxicity or bleomycin's pulmonary toxicity by local delivery of the drug. The second and third indications are exemplified by local delivery of bisphosphonates that are retained in locally effective doses that would be inconvenient or difficult to achieve by regular systemic administration of the drugs. This particularly is important because these drugs have a direct dose-response relationship and have reduced bioavailability as oral bisphosphonates.[7,8]

Alternatives to PMMA have great appeal as local delivery media,[2,3,6,12,23,35,39,41] yet none matches the successful blend of strength, compatibility, and ability to reconstruct bone defects while delivering pertinent drugs. The Food and Drug Administration has approved PMMA for skeletal reconstruction and fixation of prostheses that are used in reconstructive orthopaedic and oncologic surgeries. It is widely available, inexpensive, convenient, and orthopaedic surgeons are comfortable with it. It is not widely appreciated, however, that the commercial formulations of PMMA differ significantly in their composition. Not only the constituents, activators, and potentiators, but the cement's particle size can differ significantly and can have a major influence on the final mechanical and drug elution properties of the cement (Table 1).

Mixing techniques alter each cement's mechanical properties and how effectively drug elution occurs.[13,38,46] Inclusion of multiple drugs (including contrast agents such as $BaSO_4$) may alter the elution profiles of the drugs from cement.[13,38,46]

There is an opportunity to engineer cement composition by changing the particle size or pore size, or adding copolymers.[51] Failure rates are higher with than without metastatic disease. Wedin et al[59] noted as overall local failure rate of 11% and a median time to failure of 8 months in 192 patients treated for metastatic lung cancer. They also reported that treating pathologic fractures of the long bone was most frequent in patients with kidney cancer 24% and in patients with diaphyseal and distal femoral lesions 20%. Hosono et al[33] reported local recurrence in 24% of 90 patients with vertebral replacements treated with standard intralesional tumor excision and reconstruction with a ceramic spacer. Recurrence was 0% in patients with lung cancer and 50% in patients with renal cancer, emphasizing that the longer that the patients will live postoperatively, the greater their chance for having local failure.[33] Obviously, patients with the potential to survive

TABLE 1. Composition of Popular Cements

Component	Simplex P	Zimmer Regular	Palacos R
Liquid monomer	20 mL	20 mL	20 mL
MMA monomer	97.4% v/v	99.25% v/v	18.424 g
N,N-DMPT	2.6% v/v	2.75% v/v	0.376 g
Hydroquinone	75 ± 15 ppm	75 ± 10 ppm	unspecified
Chlorophyll	—	—	0.4 mg
Powder polymer	40 g	40 g	40 g
PMMA	15.0	89.25	—
MMA-ST	75.0	—	—
MMA-MA	—	—	33.9–33.4 g
BPO	—	1.2–2.5	0.20–0.64 g
$BaSO_4$	10.0	10.0	—
ZrO_2	—	—	5.94 mg

MMA = methylmethacrylate, v/v = volume per volume, DMPT = dimethyl-p-toluidine, ppm = parts per million, PMMA = polymethylmethacrylate, MMA-ST = methylmethacrylate styrene copolymer, MMA-MA = methylmethacrylate-methacrylate, BPO = benzoyl peroxide (Modified with permission from Parks ML, Walsh HA, Salvati EA, Li S: Effect of increasing temperature on the properties of four bone cements. Clin Orthop 355:238-248, 1998.)

longer are the best candidates for novel therapies to avoid local failure. Tomita et al[50] also reported a disturbingly high frequency of local failure in 14 of 26 patients, 54% after traditional laminectomies and excisions of metastatic carcinomas. They highlighted the rapid tumor recurrence within 6 months that occurred in their patients. It is reasonable to conclude that patients with a potential survival of at least 3 to 6 months have the potential to be helped by rationally-designed local drug delivery that prevents local disease progression, resorption of surrounding bone, and failure of the pain-relieving bone reconstruction.

Anticipating the potential value of drug delivery in PMMA for appendicular and axial spinal applications, a series of preclinical experiments was done. We specifically tested the effect of doxorubicin and pamidronate, individually and collectively, on the mechanical properties of PMMA, and how a combination of these drugs affected the elution of each drug from the cement. The data encourage moving into clinical Phase I and Phase II studies of the various combinations.

METHODS

Commercially-available Surgical Simplex® cement donated by Stryker (Osteonics Howmedica Corp, Mahwah, NJ) with various combinations and concentrations of added drug was used for all investigations. Pharmacia Italia (Milan, Italy) donated the doxorubicin, and Dr. William Bornmann of the Memorial Sloan Kettering Cancer Center's Organic Synthesis Laboratory (New York, NY) synthesized the pamidronate. Infrared and mass spectroscopy confirmed the purity of the pamidronate.

We pulverized the drugs using a mortar and pestle to reduce their particle size. Table 2 shows the dual drug levels that were formulated with 40 g of PMMA powder. The drug quantity was added to the cement powder and blended in a fluted rock tumbler for 30 minutes. The cement-drug blend was transferred to a Howmedica Artisan vacuum mixer Stryker Osteonics (Howmedica Corp). The cement catalyst was cooled in an ice bath for 5 minutes and then was poured over the cement blend within the mixer. Vacuum was applied at 20- to 26-inch Hg and mixing occurred at two revolutions per second for 60 seconds. Cement test cylinders, 11.7 mm high by 6 mm diameter, as specified by ASTM standards for compression properties of rigid plastics[1] were prepared by injection molding. The cylinders were removed from the mold and both ends were sanded to create smooth, parallel surfaces for testing. During their preparation, care was taken to avoid air bubble entrapment in the cement. Any cylinders with defects of more than 10% of the cross-sectional areas were not used.

Compression and tension measurements were done using an MTS Model 312.21 Load Frame (MTS, Cambridge, MA). Compression strength was determined using with a 500-lb load cell with a displacement rate of 1 mm per minute applied until a yield point between 1500 and 2000 N and displacement of 0.5 mm and 1.0 mm were obtained. Tension tests were done using cement fabricated into solid bowties with central dimensions of 13 × 3 mm using stainless steel molds. Tension grips were applied to each end and specimens were loaded to failure at a rate of 25 N per second.

Purity, stability, and concentration of each drug obtained from elution of the polymerized

TABLE 2. Dual-Drug PMMA Cement Formulations

Mixture Code	Doxorubicin g	Pamidronate g	PMMA powder g
A	0.5	0.5	40
B	1.0	1.0	40
C	1.5	1.5	40
E	2.0	2.0	40

cement were determined using fluorescence high pressure liquid chromatography (HPLC). The HPLC system included a Spectra System AS3000 auto sampler, P2000 pump (Thermo Separation Products Inc, Rivera Beach, FL), a Waters 470 scanning fluorescence detector (Millipore Corp, Milford, MA), and a Chromegabond WRC18 column (Chromega Columns, ES Industries, West Berlin, NJ). Doxorubicin was measured using an excitation wavelength of 480 nm and emission wavelength of 560 nm, whereas pamidronate was measured using a wavelength of 340 nm and an emission wavelength of 456 nm. Elution experiments were done using compression test cement cylinders placed into vials containing 4 mL Dulbecco's phosphate buffered saline (PBS; MSKCC Media Laboratory, New York, NY). The vials were arranged in a shaker oven at 37° C, and 200 rpm. Phosphate buffered saline was exchanged every 24 hours for 11 days and then every 96 hours until Day 19, and then kept in PBS for 6 months. Compression testing was done on these specimens, results were compared with cylinders that did not undergo elution experiments.

All statistical analysis was done using the Student's t test.

RESULTS

Added drug affected the cement strength, based on the amount of drug added, the type and duration of storage, and the method used for the mechanical testing. Compression testing showed that the ultimate strength was greater in control cement no drugs than with any drug combination, but the modulus was not affected by as much as 4 g total drug added (Fig 2). Cement strength varied based on the method and duration of storage. Nevertheless, excellent strength was retained in compression and tension (Fig 3). The resulting preparations still retain as much as 87% of their compressive and tensile strength after 6 months of wet storage.

Drugs that eluted from the cement were tested for preservation of their chemical structure. The pamidronate and doxorubicin PMMA elution chromatograms were identical to the native compound chromatograms, establishing that the exothermic polymerization process did not chemically change these drugs. The doxorubicin chromatogram suggests that the compound breaks down in the presence of the PBS. Breakdown of pamidronate in PBS was not observed.

Pamidronate and doxorubicin elution was related directly to the amount of drug mixed into the cement. The majority of drug eluted during the first 24 hours, smaller amounts eluted during the next 2 days, and a small amount eluted during the next several weeks. This was approximately the same for each of the formulations tested. The elution time of pamidronate from the dual drug formulations had a similar profile as seen from the

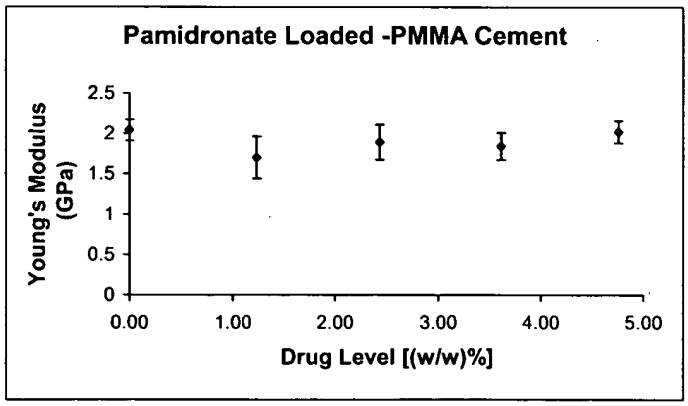
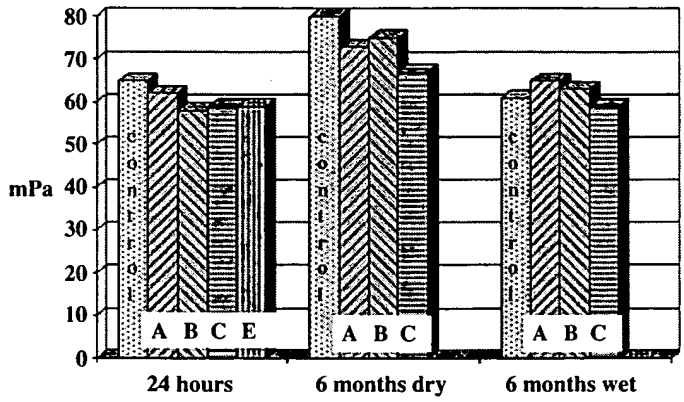


Fig 2. The graph shows Young's modulus of PMMA containing different amounts of pamidronate in 40 g Simplex. In distinction to changes in strength, there was no statistically significant difference in the modulus over the range tested (as much as 2 g pamidronate in 40 g Simplex). GPa = giga Pascals.



A= 0.5g doxorubicin + 0.5 g pamidronate; B= 1.0 g doxorubicin + 1.0 g pamidronate; C= 1.5 g doxorubicin + 1.5 g pamidronate; E= 2.0 g doxorubicin + 2.0 g pamidronate

Fig 3. The bar graph shows compression testing results of dual drug cements at varying drug concentrations. The control cement lost 7.1% of its compression strength after 6 months of dry storage. This was not statistically significant. The maximal concentrations of additives caused a reduction of ultimate strength of 8.5% after 1 day and 13.3% after 6 months of wet storage. This was not statistically significant.

pure drug, and the cumulative drug elution was not significantly different. Figure 4 shows the elution profile of pure pamidronate and the dual drug formulation of pamidronate and doxorubicin. When combined, the pamidronate eluted faster under these testing conditions. The elution of $\frac{1}{2}$ of the pamidronate from the combined doxorubicin and pamidronate cement occurred in less than 24 hours, whereas it took approximately three times as long when pamidronate was the only additive in the cement.

DISCUSSION

We established that PMMA has strength within FDA specifications when it contains as much as 2 g doxorubicin, pamidronate, or both. These drugs elute in amounts that may be biologically active. Cement with antineoplastic and antiresorptive drugs has enough strength for reconstructive purposes and may retard loss of surrounding bone that contributes to prosthetic failure. The concept of combining structural and biologic drug delivery purposes has succeeded in other organ systems, for example in preventing restenosis of coronary grafts. It may succeed similarly in preventing reconstructive failure in patients treated for pathologic fracture. Before using this combination product clinically, it is necessary to define the purpose of each component to treat patients with bone metastases, review the failure rate of existing strategies, understand how cement and drugs may interact, and scrutinize the existing preclinical data.

Acrylic cement has had widespread use to secure implants, to augment fracture fixation, and to fill bone voids. It also has been beneficial in the treatment of pathologic fractures of the axial and appendicular skeleton. Harrington[27] and Harrington et al[28] applied PMMA to pathologic fracture fixation to stabilize implants, retard bleeding, and control local tumor growth.

Scoville et al[45] described the use of acrylic cement as a convenient, effective method for replacement and internal fixation of the vertebral body, extending the use of cement as a supplement to posterior spine stabilization. Other surgeons extended and refined the method using PMMA for cervical spine stabilization of vertebrae after treatment of metastatic disease.[18,54] Cement reconstructions had significant mechanical limitations when Wang et al[55] tested them in

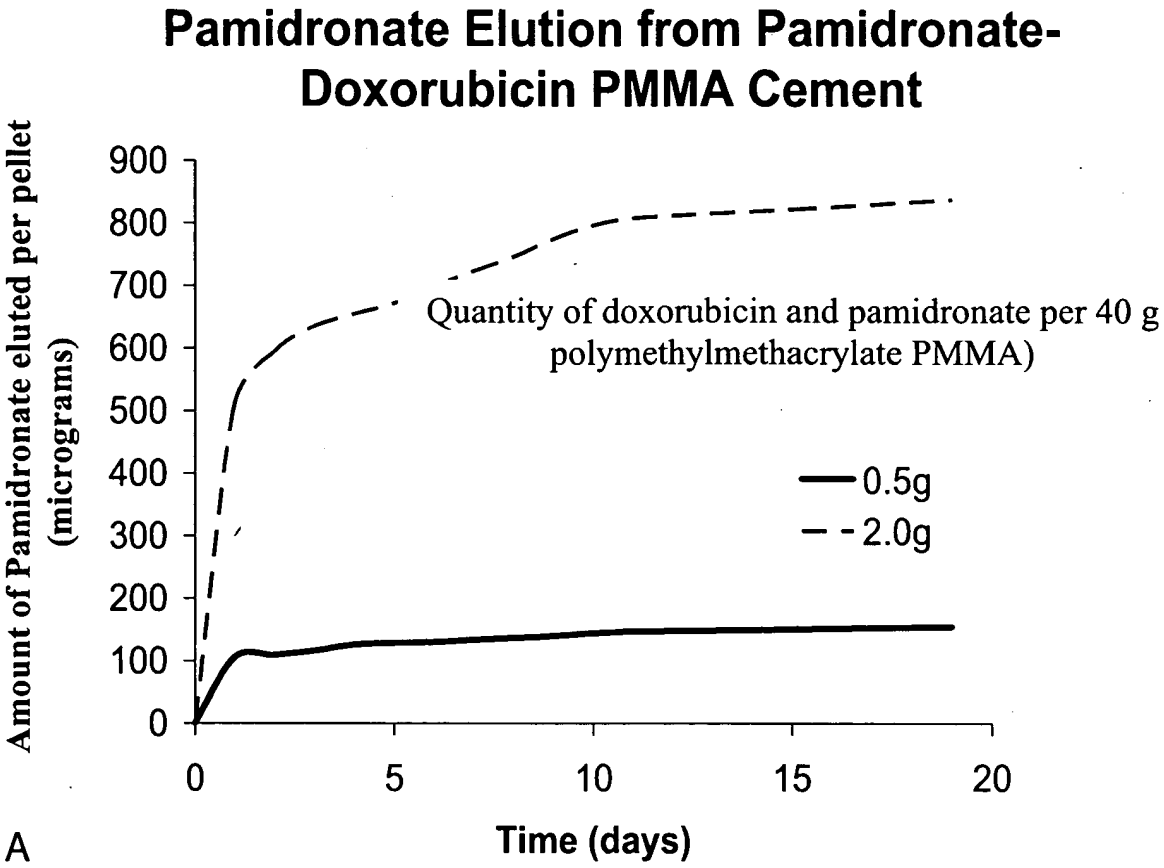


Fig 4A–B. (A) The graph shows the pamidronate elution curve. The amount of pamidronate that elutes varies directly with the concentrations of drug present. This relationship holds true in the presence of doxorubicin. The percentage of drug that elutes during the initial phase may differ based on the drug concentrations. (B) The graph shows the pamidronate elution curves for single-drug and dual-drug PMMA formulations. Pamidronate elution is greater when it is combined with doxorubicin in the cement.

extension or tension. Compression tests, however, confirmed the valid use of the method. Harrington[27] extended the indications for the use of PMMA as an adjunct to stabilize the thoracic and lumbar spine after anterior decompression, areas of predominantly compressive loads. He reported the mechanical success in 72 of 77 such constructs. Six additional patients had regional tumor progression that compromised the spine stability during the next 5 to 95 months. The technique had similar success in long bone pathologic fracture treatment.[28] The method was shown to be convenient and inexpensive, but vulnerable to failure because of additional bone destruction from local cancer progression. Therefore, disease control is necessary for long-term success. Local antineoplastic drug delivery would be a natural extension of the method.

Because drugs such as doxorubicin are antibiotics, the experience of antibiotics additives in cement is instructive. Buchholz[9] and Buchholz and Engelbrecht[11] popularized the use of antibiotic in cement using 2 g gentamicin in 40 g Palacos® cement (Biomet, Warsaw, IN) for the treatment of prosthetic infections. They were able to cure 78% of 263 established deep prosthetic infections by achieving a bactericidal concentration of antibiotic drug in the wound

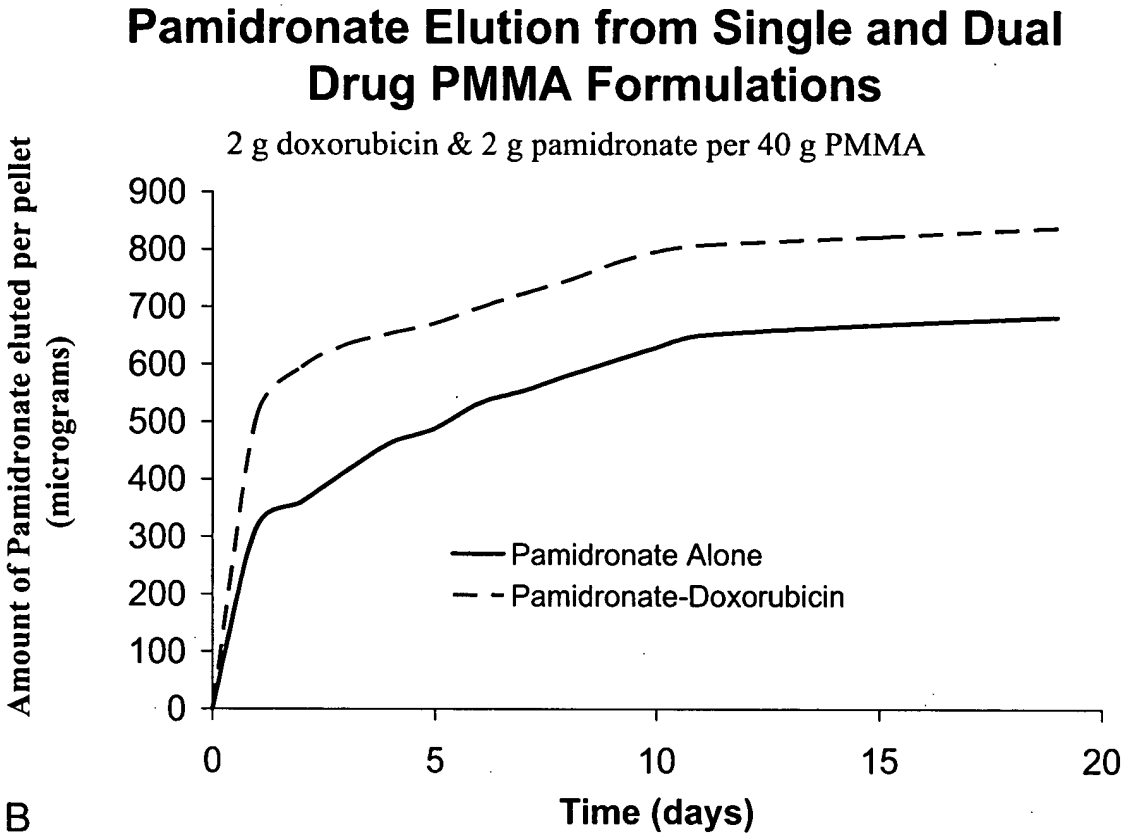


Fig 4A–B. (continued)

and at the critical bone-cement interface. It has become the standard approach to treat patients with arthroplasties infected joint. The method then was applied successfully prophylactically to patients with uninfected, primary joint arthroplasties and decreased the infection rate to 0.09%. Extensive work has been done to define the elution profile of most popular antibiotics that cover the spectrum of organisms that commonly cause periprosthetic infections. Interestingly, different cement formulations resulted in different elution profiles.[19,40] Generally, the release of antibiotic was greater for Palacos® than for Simplex P®. The authors reached conflicting con-clusions regarding the reasons behind the different elution from the cement. Some thought that electron microscopy showed greater porosity that was responsible for increased drug elution,[40] and others contended that spaces in the cement were not interconnected resulting in less effective surface area from which drug could elute.[19] The unifying principle was that the microstructure of the cement influenced the amount and timing of drug release from cement.

Various factors affect the cement microstructure and must be controlled to optimize drug elution without excessively weakening the cement. The method used to prepare the cement influences the porosity and mechanical properties of the cement. Eyerer and Jin[21] showed that the amount of air introduced into hand-mixed cement can be reduced to less than 5% by limiting the number of stirring beats used to mix the cement. Vacuum-mixing techniques suggested by other investigators also have reduced cement porosity to as little as 0.1%.[60] Reduced porosity translated into improved compressive and tension test results and better fatigue resistance in vacuum-mixed cement compared with hand-mixing or centrifugation methods. Mechanical testing results

differed based on the time to testing and the storage conditions wet versus dry). Nevertheless, the cement strength still was high (56.9 MPa) and probably well in excess of what is required for clinical applications. These results extend the observations in the literature that multiple mechanical parameters should be used to properly assess the effect of any additive to bone cement.

All drugs or other additives weaken cement and influence which type of cement is best for a given application: in this case, the treatment of patients with pathologic fractures. Although decreased porosity is desirable to maximize the strength of cement, it retards drug elution. Kuechle et al[38] reported that vacuum mixing decreased the release of vancomycin, amikacin, and other antibiotics by 50% compared with hand mixing. Therefore, porosity directly benefits drug elution while weakening the cement. Because the bones affected by pathologic fractures are deficient and heal poorly, if at all, a strong durable, rigid construct is needed. Mixtures of bioabsorbable substances in PMMA or HA cements may increase drug delivery while preserving some mechanical strength. Polymethylmethacrylate is the best cement for this purpose that is available currently, so it remains the most suitable medium to deliver drug. The ideal balance that allows drug delivery without critically affecting cement strength has not been worked out.

Dependable elution is needed for any local drug delivery system. The picture is clouded when multiple drugs are added to the cement, as is common in clinical practice. The current investigations are helpful in defining the magnitude of that effect and documenting the interactions that occur when multiple drugs are included in the cement. The influence of multiple drugs on their respective elution profiles has not been reported for antineoplastic agents, but has been reported for various antibiotic combinations. Different elution efficiency was reported, based on the testing conditions and the antibiotics tested.[38,52] One study showed that there was a 68% increase in tobramycin elution when the drug was combined with vancomycin in PMMA.[42] More impressive was the 103% increase in vancomycin release when used in the antibiotic combination.[42] Penner et al[42] concluded that the elution of one agent exposed greater surface area and facilitated additional elution of the other drug in an opportunistic fashion. These complex interactions have not been examined in other classes of drugs until now. The current experiments showed that the addition of a second drug doxorubicin increased the elution of pamidronate somewhat, but to a much smaller degree than the work of Penner et al[42] with antibiotics where combinations enhanced drug delivery. There is no obvious explanation for these results. Seemingly, each drug combination must be tested individually for its drug elution profile even though the decrement in mechanical properties is fairly uniform regardless of what is added to the cement.

Antineoplastic and antiresorptive additives may be beneficial for use in patients with cancer. Cytotoxic chemotherapy and systemic bisphosphonates are the standard method to control metastatic cancer that extensively affects the skeletal system or has failed to respond to radiation therapy in any osseous site.[15,17,29,32,44,49] The goal is to achieve an effective drug level in the affected tissues. Although this can be achieved by the systemic administration of the drug, healthy organs are exposed to the drug and toxicity can ensue (cardiac damage from doxorubicin or pulmonary damage from bleomycin). Systemic bisphosphonates can cause renal toxicity and should be used with care in patients with renal or prostate cancer. Local delivery of effective drugs may minimize the toxicity while maximizing the beneficial antineoplastic and antiresorptive bone effects.

Various chemotherapeutic agents may be effective when administered locally. Hernigou et al[30] first added chemotherapeutic agents to PMMA. Methotrexate (MTX) has been the most frequently tested because it has an established benefit for patients with osteosarcoma and local tissues tolerate the drug. Methotrexate elution after 15 days in vitro still was 100 times the LD50 for cultured osteosarcoma cells. The drug was

unaltered and approximately 10% eluted during the first 18 hours.[30] Some authors have reported important differences in the percentage of drug that elutes during in vitro experiments.[58] After 6 months, elution was up to 6% of MTX, 3.3% of cisplatinum, and 3.4% of 5-fluorouracil.[58] The results cannot be generalized for other antineoplastic agents. Similar to the findings regarding antibiotic elution, each cement formulation tested had a different elution profile.[58] Hernigou et al[30] tested the effectiveness in vivo. Methotrexate (> 150 mg) cement improved survival and reduced local recurrence of osteosarcoma in naturally-occurring tumors in dogs. The only surgery that the animals received was intralesional, so almost universal local recurrence was expected, yet only three of 17 dogs had local recurrence, attesting to a beneficial effect. However, there was a high incidence of wound healing difficulties (four of 17 dogs).[31] Other authors reached similar conclusions using MTX cement in tibias from rabbits containing experimental VX2 carcinoma.[56,57] In these experiments, established tumor was excised intralesionally by curettage and MTX cement was implanted. The number and frequency of pulmonary metastases were reduced, and there was a significant reduction of osteoclastic bone resorption in the tibia. The authors concluded that similar treatment might be a useful adjuvant in the treatment of pathologic fractures of long bones.[56,57]

Local concentrations, inconceivable by other means of drug delivery, can be achieved from antineoplastic agents in the cement. Kim et al[37] reported 130 to 10,000 times the minimum inhibitory concentration of MTX for osteosarcoma cells in their 4-week experiment. Because the drug levels reported were supertherapeutic, lower amounts of drug would be expected to be effective and more economical. The wide therapeutic ratio is an important advantage for MTX.

In our experiment, the effectiveness of the doxorubicin that eluted from the cement was difficult to evaluate because of significant breakdown of the drug in PBS. The findings show the need to understand the chemical stability of the solute within the elution solvent. However, there is no reason to think that the stability of the doxorubicin in the PBS is different from that in circulating plasma. Despite of these technical problems that artificially lowered doxorubicin concentrations, the drug levels we measured after 24 hours of elution exceeded the LD50 established by the NCI during the evaluation of numerous human cancer cell lines, including nonsmall cell lung cancer, renal, breast, and prostate cancer.[37] Potentially, effective drug levels also may be present at later analysis points. Local drug delivery is rational to improve local cancer control.

The convenience of a solitary dose, administered at the time of surgery, should be emphasized. Although the course of bone uptake was not studied, it is reasonable to assume that locally deliver a shorter time than systemic drug administration during a more protracted period.

Polymethylmethacrylate is the strongest, most forgiving, and adaptable system for use in patients with metastatic bone disease. Other cements may have value in mechanically protected sites. For example, calcium phosphate cement containing 20% cis-diaminedichloroplatinum (CDDP) produced effective sustained release of drug.[48] The in vitro cumulative release ratio was greater than 60%, and a release rate of 0.1 mg/day was maintained. Rabbits that received 10% CDDP showed that the platinum (Pt) concentration in local bone marrow averaged 3200 μg/g tissue, 6 weeks after implantation, yet did not prevent local bone formation.[48] Bioabsorbable polymers also may be able to deliver systemically effective levels of chemotherapeutic agents, but the delivery systems lack the structural strength needed to treat pathologic fractures or skeletal metastases in humans.

It remains to be seen how well combinations of multiple antineoplastic or antiresorptive drugs in cement will perform in vitro and in vivo. This investigation evaluated the dose response relationships of two drugs 1/N pamidronate and doxorubicin in terms of their elution and mechanical profiles. The dual drugs showed better elution of doxorubicin and similar elution of pamidronate.

This suggests a dual drug elution benefit, although the dual drug cements had a modestly lower ultimate strength. Although this effect is similar to that reported for antibiotic combinations in cement,[13,26] it is desirable to define the relationship for each drug combination used. Risk of failure of any reconstructive construct is related to patient diagnosis and survival, local disease progression, and the strength of the construct. Cement additives weaken the PMMA somewhat, so the cemented construct could fail during the patient's limited remaining life. This study shows that the weakness is small when 2 g or less of drug is added, but fatigue testing of the cement is needed before these cement drug combinations should be used clinically. Because the cement complies with FDA standards for cement strength, clinical failure is unlikely in the population of patients with metastatic cancer. Clinical Phase I and Phase II trials are needed for antineoplastic and antiresorptive drugs.

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